PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Robin L. Polt
Edward J. Bilsky

Date: March ___, 2007

Serial No.: 10/540,443

Group Art Unit: 1639

Filed: 06/22/2005

Examiner: Christopher M. Gross

Title: GLYCOSYLATED ENKEPHALIN AGENTS

Docket No.: 920214.00005

DECLARATION OF ROBIN L. POLT UNDER 37 CFR §1.132

Mail Stop Amendment
Commissioner for Patents
P O Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Robin L. Polt, on oath declare and sayeth that:

1. I am the same Robin L. Polt who is one of the named inventors of the above-identified patent application. I make this declaration in support of that patent application.

2. I am a professor in the Department of Chemistry and Medical Pharmacology at the University of Arizona. I have worked as a scientist specializing in the general area of glycosides and peptides for 18 years. I have published extensively in this area. A copy of my *Curriculum Vitae* is attached as Exhibit A.

3. I have reviewed the above-identified application and understand the nature and scope of the invention claimed therein. I have also reviewed the Office Action issued by the U.S. Patent and Trademark Office (USPTO) on December 5, 2006 for this application. I understand that currently Claims 1-10 are in-part rejected as being (i) inherently anticipated by

Horvath et al. (1986) *Synthesis* 3:209-211 as evidenced by Egelton et al. (2001) *J. Pharmacology and Experimental Therapeutics* 299:967-972 (see page 4 of the current Office Action); and (ii) rendered obvious by Roques et al. (US Patent 4,407,794) in view of Mitchell et al. (2001) JOC 66:2327-2342 (see page 9 of the current Office Action).

4. I respectfully disagree with the Examiner's rejections I submit this Declaration to show that our claimed invention exhibits properties surprisingly and unexpectedly superior to that which was found in the scientific or patent literature at the time of filing the application. Thus, I believe the above-identified documents do not anticipate or render obvious the claimed embodiments of our invention.

5. I believe that Horvath discloses the synthesis of a series of peptides that are glycosyl pseuro-ureas. It is important to note that these compounds are not glycopeptides, but rather C-terminal glycosyl derivatives that are typically referred to as neoglycopeptides. Although two of the peptide sequences contain the YGGF motif, and may be regarded as enkephalin analogues, the paper is strictly concerned with the synthesis of these neoglycopeptide compounds, and does not discuss opioid binding, pharmacology or any effects on the bio-distribution of these compounds, or the blood-brain barrier.

6. In regards to the Mitchell paper, I wish to point out that I am an author on that paper and the research was conducted in my laboratory. I understand that Mitchell discloses synthetic methods related to the synthesis of amino acid glycosides and glycopeptides. In the introduction of that paper we indicate our motivation for the synthesis of the glycopeptides, but do not disclose the requisite details required to achieve penetration of the blood-brain barrier with glycopeptides.

7. Based on my experience, one skilled in that art could not have read these documents together and arrived at our glycosylated enkephalin peptides because the claimed methods and peptides are not logically deducible from the teachings of the cited documents. Thus, I believe that for the above-stated reasons neither Horvath nor Mitchell, alone or in combination inherently anticipate or render obvious our invention.

8. As to the Roques patent, I believe that it discloses the use of a few different D-amino acids in the 2nd position (see, Table 1 and column 1, Claim) and L-threonine or L-serine in the 6th position of enkephalins in order to enhance binding affinity to the opiate receptor. These peptides are typically referred to as DTLES, DSLET. Roques' compounds are common enkephalin analogues, and have been used in diverse biochemical studies. These compounds have no utility as pharmaceuticals due to their poor biodistribution and inability to penetrate the blood-brain barrier to reach the opiate receptors in the brain.

9. Again, as I stated above, Mitchell discloses only synthetic methods. No biological data is disclosed in this paper. The peptide sequences described in this paper are all cysteine-containing compounds related to DPDPE, and not the Roques' compounds. Therefore, based on my experience, one skilled in that art could not have read these documents together and arrived at our glycosylated enkephalin peptides because these peptides are not logically deducible from the teachings of the cited documents. Thus, I believe that neither Horvath nor Mitchell, alone or in combination render our invention obvious.

10. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Further declarant sayeth not.

Dated: March 3, 2007

Robin L. Polt

Robin L. Polt
Curriculum Vita

Chronology of Education

1972 - 1974	Purdue University (interrupted by military service)
1976 - 1981	Indiana University - Purdue University at Indianapolis B.S. Chemistry
1980 - 1986	Columbia University, Ph.D. Chemistry, 1986
1986 - 1988	Eidgenössiche Technische Hochschule (ETH), Zürich, Switzerland. Post-doctoral study

Dissertation Advisor: Gilbert J. Stork

Dissertation Title: *PART I: Lithioenamines in Synthesis. PART II: Metallation Under Conditions of Poor Solvation. PART III: Trans-hydrindanones via Zirconium Catalyzed Michael Reaction. Synthesis of a Key Intermediate to Retigeranic Acid.*

Major Fields: Organic Synthesis, Synthetic Methods

Chronology of Employment

1975 - 1978	United States Army	COMSEC Cryptographic Communications Repair
1979 - 1981	IUPUI	Teaching Assistant
1980 -1981	IUPUI	Research Assistant
1981	Stauffer Chemical Co.	Research Assistant
1981 - 1982	Columbia University	Teaching Assistant
1982 - 1986	Columbia University	Research Assistant
1986 - 1988	ETH, Zürich	Postdoctoral Fellow with Dieter Seebach
1988 - 1994	University of Arizona	Assistant Professor Department of Chemistry
1994 - 2000	University of Arizona	Associate Professor

		Department of Chemistry
2000 -	University of Arizona	Professor Department of Chemistry

Honors and Awards

National Merit Four Year Scholarship (1972)

Purdue University President's Freshman Fellowship (1972)

Student Representative to the Board of Trustees for Purdue University (1980 - 1981)

IUPUI Student Activities Award (1981)

IUPUI Science Scholar Award (1981)

Rhom & Haas Graduate Summer Fellowship @ Stauffer Chemical Co. Labs (1981)

Sigma Xi

National Science Foundation Pre-Doctoral Fellowship (1981—1984)

National Institutes of Health Post-Doctoral Fellowship (1987—1989)

Who's Who Among America's Teachers (multiple year honoree)

Who's Who in Science and Engineering

GenCorp Award in Chemical Synthesis (1998)

Service

Local/State

Member, Governor's Strategic Partnership for Economic Development, Biotechnology Cluster, State of Arizona.

Chair, Southern Arizona Section, American Chemical Society (1997—98)

General Chair, 10th C. S. Marvel Symposium, Tucson, AZ (1993—1994)

Scientific Advisor, Pharos Pharmaceuticals, Green Valley, AZ (1996—1999)

ACS Rocky Mountain Regional Steering Committee (1996—2000)

National/International

14th Rocky Mountain Regional Meeting of the American Chemical Society 15—18 March 1998, Tucson, AZ, *General Chair & Organizer*

Symposium on Carbohydrate Chemistry, 5th Chemical Congress of North America, 11—15 November 1997, Cancun, Mexico, *Co-Organizer*

Awards Committee, American Chemical Society
2001—
Bioorganic and Natural Products Study Section, National Institutes of Health
June 2001, Bethesda, MD

Chemistry/Biophysics Fellowship Panel, National Institutes of Health
July 2002, Bethesda, MD

Program Officer Rotator, Organic and Macromolecular Chemistry Program, National Science Foundation
5 August 2002 — 4 August 2003, Arlington, VA

Editorial Board, *Current Drug Delivery*
Bentham Science Publishers, http://www.bentham.org/cdd/index2.htm
June 2003—

Departmental Service

1994-95

Graduate Program Committee (1993—1995)
Undergraduate Program and Curriculum Committee
Marvel Symposium Committee
Library Committee

1995-1996

Graduate Recruiting Committee, Chair
Space Committee
Library Committee

1996-97

Graduate Recruiting Committee, Chair
Space Committee
Library Committee
Peer Review Committee
Jr. Faculty Advisory Committee (Rainier)

1997-1998

Rocky Mountain Regional Meeting Org. Committee, Chair
Graduate Recruiting Committee
Mass Spectroscopy Facility Oversight Committee
Jr. Faculty Advisory Committee (Rainier)

1998-1999

Graduate Program Committee
NMR Facility Oversight Committee
Mass Spectroscopy Facility Oversight Committee
Jr. Faculty Advisory Committee (Rainier)

1999-2000

Graduate Program Committee
Jr. Faculty Advisory Committee (Rainier)

2000-2001

Organic Division Head (Steering Committee)
Organic Search Committee
Jr. Faculty Advisory Committee (Rainier)
Peer Review Committee

2001-2002

Organic Division Head (Steering Committee)
Departmental Needs Committee (Dean Ruiz Committee)
Department Head Search Committee
Jr. Faculty Advisory Committee (Aspinwall)
Jr. Faculty Advisory Committee (Ghosh)

2002-2003

NSF Rotation (relieved of assignments)

2003-2004

Graduate Recruiting Committee
Staff Review Committee
Jr. Faculty Advisory Committee (Aspinwall)
Jr. Faculty Advisory Committee (Ghosh)

2004-2005

Jr. Faculty Advisory Committee (Aspinwall)
Jr. Faculty Advisory Committee (Ghosh)

College of Science Committees

Curriculum Review Committee (1996—1997)
Protein Sequencing Facility Oversight Comm., Chair (2001-2002)
Departmental Needs Committee (2001-2002)
Chemistry Department Head Search Committee (2002)

University Committees

Undergraduate Admission Appeals Committee (2000—2001)

Other Intramural Committees

Synthetic Core Facility of the University of Arizona Center for Toxicology (1993—)
Breaking the Silences: A Faculty-Student Action Project for Graduate Women in Science and Mathematics, NSF Project, Dr. Banu Subramaniam, P.I. (1996—1997)

Extramural

American Chemical Society, Organic & Carbohydrate Divisions
Southern Arizona Section of the American Chemical Society, (served as Chair, Chair Elect, Secretary, Treasurer)
A.C.S. Rocky Mountain Regional Steering Committee
Southern Arizona Columbia Club (Vice President)

Reviewer - Journals

Journal of the American Chemical Society
Journal of Organic Chemistry
Journal of Natural Products
Tetrahedron
Tetrahedron Letters
Bioorganic and Medicinal Chemistry Letters
Organic and Bioorganic Chemistry (Perkin Transactions I)
Chemical Reviews
Analytical Biochemistry
Journal of Peptide Research (Int. J. Peptide and Protein Res.)
Carbohydrate Research
Journal of Carbohydrate Chemistry

Reviewer -Grants

American Chemical Society - Petroleum Research Foundation
National Science Foundation
Bio-Organic and Natural Products Study Section – NIH (ad hoc)
Pre- and Post-Doctoral Fellowship Review Study Section — NIH
Tobacco Related Disease Research Program — State of California
Research Corporation
U.S. Department of State

Publications

Chapters

The Conformational Properties of Glycopeptide Enkephalin Analogues in Solution, Determined by NMR and Molecular Modeling. [§]B. Lou, L. Szabò, M. Shenderovich, R. Polt and V.J. Hruby *Peptides, Chemistry, Structure and Biology.* Kaumaya, P.T.P.; Hodges, R.S. (Eds.), Escom, Leiden, Netherlands **1995**

• ¶ *9-Fluorenylmethoxycarbonylchloride (Fmoc).* [§]**Robin Polt** *Encyclopedia of Reagents for Organic Synthesis,* Leo Paquette, (Ed.), John Wiley & Sons, Chichester **1995**

• ¶ *Amaryllidaceae Alkaloids with Antitumor Activity.* [§]**Robin Polt** *Organic Synthesis: Theory and Applications, Vol. 3* pgs 109—148 Tomas Hudlicky, (Ed.) JAI Press, Inc. **1996**

† *The Effect of Glycosylation on the Uptake of an Enkephalin Analogue into the Central Nervous System.* Sarah A. Williams, Thomas J. Abbruscato, Lajos Szabo, [§]**Robin Polt**, Victor Hruby, and Thomas P. Davis, pp 69 - 77, *Biology and Physiology of the Blood-Brain Barrier,* Couraud & Scherman, Eds., Plenum Press, New York **1996**

• *Synthesis and Pharmacology of O-Linked Glycopeptide Analogues: A New Class of Opioid Analgesics.* [§]**Robin Polt**, Lajos Szabo, V.J. Hruby, T.P. Davis, F. Porreca and H.I. Yamamura *Innovation and Perspectives in Solid Phase Synthesis & Combinatorial Libraries* pp 277—280 Roger Epton (Ed.), Mayflower Scientific Ltd, Birmingham, England, UK **1997**

• ¶ *Synthetic Methods for Glycopeptides.* [§]**Robin Polt**. *Carbohydrate Chemistry,* Geert-Jan Boons, (Ed.), pp 221—242. Chapman and Hall, London **1998**

• ¶ *Benzophenone Imines of α–Amino Acids as Electrophiles,* [§]**Robin Polt** *Amino Acid Derivatives: A Practical Approach,* p.p. 101—114, G.C. Barrett, (Ed.) Oxford University Press, Oxford **1999**

• † *Glycopeptide Analgesics Derived from Enkephalins,* Chapter by **Robin Polt** and Scott A. Mitchell in *Glycoscience: Chemistry and Chemical Biology,* 2355—2392, B. Fraser-Reid, K. Tatsuta, J. Theim, (Eds.) Springer-Verlag GmbH, Heidelberg **2001.**

• ¶ *Glycopeptide Analgesics,* Chapter by Michael M. Palian and **Robin Polt** in *Drugs of the Future* **26***(6),* 561-576 **2001**

Refereed Journal Articles

** *A Mild and Efficient Route to Schiff Base Derivatives of Amino Acids.* Martin J. O'Donnell & **Robin L. Polt** *J. Org. Chem.* **47**, 2663—2665 (1982)

* *X-ray Crystal Structure of N-(2-lithiocyclohexenyl)-N,N', N'-trimethyl-1,3-propanediamine: A Pentavalent Lithium?* **Robin L. Polt**, Gilbert Stork, Gene B. Carpenter & Paul G. Williard *J. Am. Chem. Soc.* **106**, 4276—4277 (1984)

** *Preparation of an Electrophillic Glycine Cation Equivalent and Its Reaction with Heteroatom Nucleophiles.* Martin J. O'Donnell, William D. Bennett & **Robin L. Polt** *Tetrahedron Letters* **26**, 695—698 (1985)

* *The Deprotonation of Chelating Enamines. Direct Formation of beta-Lithioenamines.* Gilbert Stork, Christopher S. Shiner, Chi-Wen Cheng & **Robin Polt** *J. Am. Chem. Soc.* **108**, 304—305 (1986)

* *PART I: β-Lithioenamines in Synthesis. PART II: Metallation Under Conditions of Poor Solvation. PART III: Trans-hydrindanones via Zirconium Catalyzed Intramolecular Michael Reaction. Synthesis of a Key Intermediate to Retigeranic Acid.* **Robin Lee Polt**, Thesis, Columbia University (1986)

§ *Alkylation of Imidazolidinone Dipeptide Derivatives: Preparation of Enantiomerically Pure Di- and Tripeptides by "Chirality Transfer" via a Pivaldehyde Acetal Center.* **Robin Polt** & Dieter Seebach *Helvetica Chimica Acta*. **70**, 1930—1936 (1987)

§ * *Theoretical Studies on the Deprotonation of Chelating Enamines.* Gilbert Stork, **Robin Polt**, Yi Li & Kendall N. Houk *J. Am. Chem. Soc.* **110**, 8360—8367 (1988)

** *Acidities of Glycine Schiff Bases and Alkylation of Their Conjugate Bases.* Martin J. O'Donnell, W.D. Bennett, W.A. Bruder, W.N. Jacobsen, K. Knuth, B. LeClef, **Robin L. Polt**, Frederick G. Bordwell, S.R. Mrozack & T.A. Cripe *J. Am. Chem. Soc.* **110**, 8520—8525 (1988)

§ *Stereoselective Alkylation of Glycine Units in Dipeptide Derivatives. "Chirality Transfer" via a Pivaldehyde N,N-Acetal Center.* Dieter Seebach & **Robin Polt** *J. Am. Chem. Soc.* **110**, 2622—2632 (1988)

Diastereoselective Cyclization of a Glycyl-Alanine Azomethine to an Imidazolidinone: Determination of the Product Configuration by X-Ray Analysis. [§]Martin Egli, **Robin Polt** & Dieter Seebach *Chemia* **43**, 4—5 (1989)

§ *Amino Alcohols from Amino Acids: Chelation Control via Schiff Bases.* **Robin Polt** & Matt Peterson *Tetrahedron Letters* **31**, 4985—4986 (1990)

§ *O-Glycopeptides: A Simple Stereoselective Glycosidation of Serine and Threonine* Lajos Z. Szabo, Yushun Li & **Robin Polt** *Tetrahedron Letters* **32**, 585—88 (1991)

§ *Erythrose Sesqui-Acetals as Electrophiles. 2-Deoxy-C-Nucleosides from D-Glucose.* **Robin Polt** and Thusitha Wijayaratne *Tetrahedron Lett.* **32**, 4831—4834 (1991)

§ *E-1-Lithio-Alkenes in Hydrocarbon Solvent.* Matt A. Peterson and **Robin Polt** *Synthetic Communications* **22**, 477—480 (1992)

§ *Alkoxy Schiff Base—Oxazolidine Tautomerism. Solid State Structure of N-Diphenylmethylene-L-Threonine Methyl Ester.* Thusitha Wijayaratne, Nathan Collins, Yushun Li, Michael A. Bruck, and **Robin Polt** *Acta Crystallographica* **B49**, 316—320 (1993)

§ ¥ *Aluminoxy-Acetals from Amino Esters: Chirality Transfer via Sequential Addition of Hydride and C-Nucleophiles. 2-Amino Alcohols and Sphingosines.* **Robin Polt**, Matt A. Peterson and Lynn DeYoung[¥] *J. Org. Chem.* **57**, 5469—5480 (1992)

§ ¥ *General Methods for α– or β–O-Ser/Thr Glycosides and Glycopeptides. Solid-Phase Synthesis of O-Glycosyl Cyclic Enkephalin Analogues.* **Robin Polt**, Lajos Z. Szabò, Jennifer Treiberg[¥], Yushun Li & Victor J. Hruby *J. Am. Chem. Soc.* **114**, 10249—10258 (1992)

§ *Unsymmetrical Disulfides: bis-Cysteine Disulfides of meso-2,3-Dimercaptosuccinic Acid.* **Robin Polt**, Quintus Fernando, Yushun Li & Mario Rivera *Tetrahedron Letters* **33**, 2961—2964 (1992)

§ *N-Diphenylmethylene-Protected Glycosyl Acceptors. Selective Glycosylation to Form Lactosyl-threo-Ceramides.* Matt A. Peterson & **Robin Polt** *J. Org. Chem.* **58**, 4309—4314 (1993)

§ *Glycopeptide enkephalin analogs produce analgesia in mice: evidence for penetration of the blood-brain barrier.* **Robin Polt**, Frank Porreca, Lajos Z. Szabò, Edward J. Bilsky, Peg Davis, Thomas P. Davis, Robert Horvath, John M. McCormick, Henry I. Yamamura & Victor J. Hruby *Proc. Nat. Acad. Sci. U.S.A.* **91**, 7114—8 (1994)

Assesment of an <u>in</u> <u>vitro</u> blood-brain barrier model using several [Met5]enkephalin opioid analogs. S. Weber, T.J. Abbruscato, A. Lipkowski, A. Misicka, R.C. Haaseth, H. Bartosz, **Robin Polt**, L. Szabò, V.J. Hruby and [§]Thomas P. Davis *Journal of Pharmacology and Experimental Therapeutics* **261**, 1649—1655 (1993)

§ *Stereoselective synthesis of β–D-glycopyranosyl-L-serinate or -threoninate derivatives with an unusual migration.* Lajos Szabò and **Robin Polt** *Carbohydrate Research* **258**, 293—7 (1994)

New Opioid Compounds In Analgesia [§]Hruby V.J., Misicka A., Lipkowski AW., Haaseth R., Bartosz H., Qian X., Collins N., Meyer J.P., Szabò L., Polt R.,

Porreca F., Davis T., Yamamura H.I. *Regulatory Peptides* S71-S72, Suppl. 1 Feb 21 (1994)

§ *An Enantioselective Synthesis of N-Methylfucosamine via Tandem C-C/C-O Bond Formation* Dalibor Sames and **Robin Polt** *J. Org. Chem.* **59**, 4569—4601 (1994)

§ ¥ *Stereoselective Synthesis of α– or β–O-Serinyl/Threoninyl-2-deoxy-2-Acetamido-Glycosides.* Lajos Szabò, Jan Ramza, Courtney Langdon[¥] and **Robin Polt** *Carbohydrate Research* **274**, 11—28 (1995)

Determination and Metabolism of Dithiol Chelating Agents: XV. The DMSA-cysteine (1:2) Mixed Disulfide, a Major Urinary Metabolite of DMSA in the Human, Increases the Urinary Excretion of Lead in the Rat. Richard M. Maiorino, Mary M. Aposhian, Zhao-Fa Xu, Yushun Li, **Robin L. Polt** and H. Vasken Aposhian[§] *J. Pharmacol. Exp. Therap.* **267**, 1221—1226 (1993)

§ ¥ *Preparation of Monosilylacetals from Esters via iBu_2AlH Reduction and Trapping with N-Trimethylsilylimidazole. Addition of Allyltrimethylsilane to Yield Homoallylic Alcohols or Ethers.* Dalibor Sames, Yunqi Liu, Lynn DeYoung[¥] and **Robin Polt** *J. Org. Chem.* **60**, 2153—2159 (1995)

§ • *Piperidine Triols via Enantioselective Alkylation and Osmylation of Alanine Schiff Base Esters.* Dalibor Sames and **Robin Polt** *Synlett* 552—4 (1995) (Special issue dedicated to Gilbert Stork.)

† *New Method of Chemical Synthesis of O-Linked Glycopeptides.* **Robin L. Polt**, Lajos Szabò and Jan Ramza. *Postepy Hig. Med. Dosw.* **50**, 493-503 (1996). (Chem. Abs. No. 126:277763, published in Polish)

§ ¥ *N-Methylation of Amino Acids and Amino Esters via O'Donnell's Schiff Bases.* Jason Chruma[¥], Dalibor Sames and **Robin Polt** *Tetrahedron Lett.* **38**, 5085—6 (1997)

§ ¥ ¥ *Amino Acid-Derived Ligands for Transition Metals: Catalysis via A Minimalist Interpretation of A Metalloprotein.* Brian Dangel, Michael Clarke[¥], Jay Haley[¥], Dalibor Sames and **Robin Polt** *J. Am. Chem. Soc.* **119**, 10865—6 (1997)

§ *Syntheses of Iminolyxitols via Tandem Reduction-Alkenylation of O'Donnell's Schiff Bases.* Hossein Razavi and **Robin Polt** *Tetrahedron Lett.* **39**, 3371—3374 (1998)

§ *Glycosyltransferase Inhibitors: Synthesis of D-threo-PDMP, L-threo-PDMP and Other Brain Glucosylceramide Synthase Inhibitors from D- or L-Serine.* Scott A. Mitchell, Bryan D. Oates, Hossein Razavi and **Robin Polt** *J. Org. Chem.* **63**, 8837—8842 (1998)

§ *Enkephalin-Based Drug Design: Conformational Analysis of O-Linked Glycopeptides by NMR and Molecular Modeling.* Caroline Kriss, Bih-Show Lou, Lajos Z. Szabo,

Scott A. Mitchell, Victor J. Hruby and **Robin Polt** *Tetrahedron Asymmetry* **11**, 9—25 (2000)

§ ¥ *Glycosidase Inhibitors: Synthesis of Enantiomerically Pure Fuco-1-deoxy-Nojirimycin and Other Aza-Sugars from Amino Acids via Tandem Reduction-Alkenylation and Osmylation.* **Robin Polt**, Dalibor Sames, and Jason Chruma[¥] *J. Org. Chem.* **64**, 6147—6153 (1999)

§ *Asymmetric Syntheses of (-)-8-epi-Swainsonine and (+)-1,2-Di-epi-Swainsonine. Carbonyl Addition Thwarted by An Unprecedented Aza-Pinacol Rearrangement.* Hossein Razavi and **Robin Polt** *J. Org. Chem.* **65**, 5693—5706 (2000)

Structure-activity studies with novel opioid glycopeptides: Antinociception and blood-brain barrier penetration. Elmagbari N.O., Sdimid W.R., Palian M.M., **Polt R.**, [§]Bilsky, E.J. *FASEB Journal* **14**, 44 (2000)

Pharmacological strategies for developing opioid peptides as therapeutic agents. [§]Bilsky E.J., **Polt R.**, Lipkowski A.W., Misicka A., Porreca F., Hruby V.J. *FASEB Journal* **14**, 45 (2000)

§ *Catalysis by Amino Acid-Derived Tetra-Coordinate Complexes: Enantioselective Addition of Dialkylzincs to Aliphatic and Aromatic Aldehydes* Brian D. Dangel and **Robin Polt** *Organic Letters* **2**, 3003-3006 (2000)

Glycosylation improves the brain delivery of Met-Enkephalin analogs. Richard D. Egleton, Scott A. Mitchell, **Robin Polt**, Victor J. Hruby and Thomas P. Davis[§] *Brain Research* **881**, 37—46 (2000)

§ ¥ ¥ *Enkephalin Glycopeptide Analogs Produce Analgesia with Reduced Dependence Liability* Edward J. Bilsky, Richard D. Egleton, Scott A. Mitchell, Jason D. Huber[¥], Heather Jones[¥], Henry I. Yamamura, Jacqueline Janders, Thomas P. Davis, Peg Davis, Frank Porreca, Victor J. Hruby, Michael M. Palian, **Robin Polt** *J. Med. Chem.* **43**, 2586-2590 (2000)

§ ¥ *Solid-Phase Synthesis of O-Linked Glycopeptide Analogues of Enkephalin* Scott A. Mitchell, Matt R. Pratt[¥], Victor J. Hruby and **Robin Polt** *J. Org. Chem.* **66**, 2327—2342 (2001)

§ *O-Linked Glycopeptides Retain Helicity in Water* Michael M. Palian, Neil Jacobsen and **Robin Polt** *Journal of Peptide Research* **58**, 180—189 (2001)

§ *Lipo α-Amino-β-hydroxy Acids and O-Linked Glycosides: Building Blocks for Ceramyl and Glycosphingoyl Peptides.* Michael M. Palian, Robin Polt *J. Org. Chem.* **66**, 7178-7183 (2001)

Improved Blood-Brain Barrier Penetration and Enhanced Analgesia of an Opioid Peptide by Glycosylation Egleton, R.D.; Mitchell, S.A.; Huber, J.D.; Palian, M.M.; Polt, R.; [§]Davis, T.P. *J. Pharm. Exp. Ther.* **299**, 967—972 (2001)

§ ¥ *Optically Active 4- and 5-Coordinate Transition Metal Complexes of Bifurcated Dipeptide Schiff Bases.* Polt, R.; Kelly, B.D.; Dangel, B.D.; Tadikonda, U.B.; [¥]Ross, R.E.; Raisimring, A.M.; Astashkin, A.V. *Inorg. Chem.* **42**, 566-574 (2003)

§ *Glycopeptide-Membrane Interactions: Glycosyl Enkephalin Analogs Adopt Turn Conformations by NMR and CD in Amphipathic Media.* M.M. Palian, V.I. Boguslavsky, D.F. O'Brien, R. Polt *J. Am. Chem. Soc.* **125**, 5823—5831 (2003)

§ *Presence of unsaturated sphingomyelins and changes in their composition during the life cycle of the moth Manduca sexta.* D. T. U. Abeytunga, James J. Glick, Nicholas J. Gibson, Lynne A. Oland, Arpad Somogyi, Vicki H. Wysocki, and Robin Polt *J. Lipid Research* **45**, 1221—1231 (2004)

§ ¥ *New PDMP Analogues Inhibit Process Outgrowth in an Insect Cell Line.* Jacob Slavish, Lynne Oland, Donna Friel[¥] and **Robin Polt** *Bioorganic & Medicinal Chemistry Letters* **14**, 1487-1490 (2004)

Antinociceptive Structure-Activity Studies with Enkephalin-Based Opioid Glycopeptides. Nura O. Elmagbari, Richard D. Egleton, Michael M. Palian, John J. Lowery, Wendi R. Schmid, Peg Davis, Edita Navratilova, Muthu Dhanasekaran, Charles M. Keyari, Henry I. Yamamura, Frank Porreca, Victor J. Hruby, Robin Polt, and Edward J. Bilsky *J. Pharm. Exp. Therap.* **311**, 290—297 (2004)

Biousian glycopeptides penetrate the blood–brain barrier. Richard D. Egleton, Edward J. Bilsky, Gordon Tollin, Dhanasekaran Muthu, John Lowery, Isabel Alves, Peg Davis, Frank Porreca, Henry I. Yamamura, Larisa Yeomans, Charles M. Keyari, and Robin Polt *Tetrahedron: Asymm.* **16**, 65—75 (2005)

New Prospects for Glycopeptide Based Analgesia: Glycoside-Induced Penetration of the Blood-Brain Barrier. Dhanasekaran Muthu and Robin Polt *Current Drug Delivery* **2**, 59—73 (2005)

Glycopeptides Related to β-Endorphin Adopt Helical Amphipathic Conformations in the Presence of Lipid Bilayers. Muthu, D.; Palian, Michael M.; Alves, Isabel; Yeomans, Larisa; Keyari, Charles M.; Davis, Peg; Bilsky, Edward J.; Egleton, Richard D.; Yamamura, Henry I.; Jacobsen, Neil E.; Tollin, Gordon; Hruby, Victor J.; Porreca, Frank; Polt, Robin. *J. Am. Chem. Soc.* **127**, 5435—48 (2005)

Glycosylated Neuropeptides: A New Vista for Neuropsychopharmacology. Muthu, D.; Keyari, C.M.; Polt, R. *Med. Res. Rev.* **25**, 557—585 (2005)

Book Reviews

- *Glycopeptide Antibiotics.* Edited by Ramakrishnan Nagarajan *J. Am. Chem. Soc.* **117**, 7300 (1995) **Robin Polt**

- *Lipid Synthesis and Manufacture.* Edited by Frank D. Gunstone *J. Am. Chem. Soc.* **122**, 3985 (2000) **Robin Polt**

Publications in Progress...

§ ¥ *Polymeric Ketimine Supports for Solid-Phase Synthesis.* Bhaskar Tadikonda, Brian D. Dangel, Donna Friel[¥] and **Robin Polt** (in preparation)

‡ indicates contributed paper
¶ indicates reviewing the state of the field, etc.
• indicates invited manuscript
§ indicates principal author
* indicates work done as a graduate student
** indicates work done as an undergraduate student
¥ indicates contribution by an undergraduate research participant
† indicates original research - not reported elsewhere

Scholarly Presentations

International

- Oxford University, Oxford
  University of Leicester, Leicester
  University of Liverpool, Liverpool
  University of Nottingham, Nottingham
  Pfizer Central Research Laboratories, Sandwich
  3 - 12 August 1993, United Kingdom. *Amino Acid Schiff Base Synthons: β–Amino Alcohols, Sphingosines, Glycosphingolipids, Neuroactive Glycopeptides & the Blood-Brain Barrier.* §Robin Polt

- 12th International Symposium on Glycoconjugates. (GLYCO XII). 15 - 20 August 1993, Krakòw, Poland. *Synthesis of Glycosyl-Enkephalin Analogues Which Rapidly Cross the Blood-Brain Barrier to Produce Analgesia in Mice."* §Robin Polt, Frank Porreca, Lajos Szabò & Victor J. Hruby

- 3rd International Congress on Amino Acids and Analogues. 23 - 27 August 1993, Vienna, Austria. *Synthesis of Glycosyl-Enkephalin Analogues Which Rapidly Cross the Blood-Brain Barrier to Produce Analgesia in Mice. An Entirely New Class of "Designer Drugs."* §Robin Polt, Frank Porreca, Lajos Szabò & Victor J.Hruby

- 4th International Symposium on Solid Phase Synthesis & Combinatorial Chemical Libraries. 12 - 16 September 1995, Edinburgh University, Edinburgh, Scotland. *Solid Phase Synthesis of Glycopeptide Drugs.* §Robin Polt

- 5th Chemical Congress of North America. 11—15 November 1997, Cancun, Mexico. *Conformation and Dynamics of Enkephalin Glycopeptide Analogs.* §Robin Polt, Lajos Szabò, Victor J. Hruby, Caroline Kriss and Scott Mitchell

- University of Alberta Chemistry Department Colloquium. 11 January 1999, University of Alberta, Edmonton, Alberta. *Glycopeptide Drugs: Synthesis, Conformations, and the Blood-Brain Barrier.* §Robin Polt

‡ 1999 International Narcotics Research Conference Annual Meeting. 10 – 15 July 1999 Saratoga Springs, New York. *Increased Antinociceptive Activity and Blood Brain Barrier Permeability with SAM1095, A Novel Glycopeptide Enkephalin Analogue.* Jones, H.D.; Mitchell, S.A.; Egleton, R.D. Gillespie, T.J.; Davis, T.P.; Polt, R.; §Bilsky, E.J.

‡ 14th World Congress of Pharmacology, July 2002 San Francisco, CA. *Enkephalin-Based Analgesics: Influence of Membranes on Glycopeptide*

Conformation, Transport and Pharmacology. [§]Bilsky E.J., Palian, M.M., Egleton, R., Davis, P., Yamamura, H., Porreca,F., and Polt R.

‡ 33rd Annual Meeting of the Society for Neuroscience. November 2003 New Orleans, LA. *Opioid Glycopeptides With Mixed Delta/Mu Agonist Activity Produce Potent Analgesia with Decreased Stimulation of Locomotor Activity Compared to the Mu Opioid Analgesics Morphine and Fentanyl.* §Bilsky, E.J., Lowery, J.J., Viera, M., Sanborn, J., Bartlett, J.L., Winterson, B.L., Polt, R.L.

- *TIDES 6th International Peptide Technology Conference* 28-30 May 2003, Las Vegas, NV. *Synthesis and Purification of Glycopeptide Analogues of Enkephalin: Analgesia Superior to Morphine* §Robin Polt

National

- 1990 Natural Products Gordon Conference. 27 July 1990, New Hampton, New Hampshire. *A Simple β–Stereoselective Glycosylation of Serine and Threonine via a Favorable Hydrogen Bonding Pattern.* Yushun Li and §Robin Polt

- 4th Symposium on the Latest Trends in Organic Synthesis. 15 October 1990, Blacksburg, Virginia. *Tandem C-C/C-O Bond Formation via Schiff Base Complexes: Sphingosines and Glycopeptides.* §Robin Polt, Yushun Li, Matt Peterson, Lajos Szabò & Thusitha Wijayaratne

- 1991 Pacific Conference on Chemistry and Spectroscopy. 9 October 1991, Anaheim, California. *Tandem C-C/C-O Bond Formation via Aluminoxy-Acetals..* §Robin Polt, Yushun Li, Matt Peterson, Lajos Szabò & Thusitha Wijayaratne

- § 23rd NSF Workshop on Organic Synthesis and Natural Products Chemistry. 15 - 19 July 1992, Highland Lake Inn, North Carolina.- *Surface Carbohydrates: Structure, Function, Synthesis and Biosynthesis.* §Robin Polt

- 1992 Natural Products Gordon Conference. 20 - 24 July 1992, New Hampton, New Hampshire. *Synthetic Methods for Glycosphingolipids and Glycopeptides.* (Poster selected for short talk.) §Robin Polt, Matt A. Peterson & Lajos Szabò

- § 5th Symposium on the Latest Trends in Organic Synthesis. 30 September - 4 October 1992, Blacksburg, Virginia. α- *and* β-*O-Glycosides via Nucleophilic Activation by Hydrogen Bond Acceptors. New synthetic Methods for O-Linked Glycopeptides and Glycosphingolipids.* §Robin Polt, Matt Peterson, Lajos Szabò & Thusitha Wijayaratne

- § 10th Biennial Carl S. Marvel Symposium. *Enantioselective and*

Diastereoselective Processes in Organic Synthesis. 15 March 1993, Tucson, Arizona *Crossing the Blood-Brain Barrier.* [§]Robin Polt, Lajos Szabò, H. Yamamura, F. Porreca & V. Hruby

- 2nd Annual Conference on Glycotechnology Cambridge Healthtech Institute. 16 - 18 May 1994, Torrey Pines Sheraton, San Diego, CA. *O-Linked Glycopeptides: Applications and Pharmacology.* §Robin Polt

- 1994 Gordon Conference on Stereochemistry. 19—24 June 1994, Newport, Rhode Island. *Synthesis of Sphingosines, Amino-Sugars, and Aza-Sugars via Tandem CC/CO Bond Formation.* §Robin Polt, Matt A. Peterson & Dalibor Sames

- 1994 Gordon Conference on Organic Reactions & Processes 17 - 22 July 1994, New Hampton School, New Hampton, New Hampshire. *Glycopeptide Drugs and the Blood-Brain Barrier.* §Robin Polt

- 1995 Gordon Conference on Carbohydrates. (Thursday Evening Lecture). 25—30 Jun 1995. *New Methods for the Synthesis of O-Linked Glycopeptides and the Pharmacology of Glycopeptide Enkephalin Analogs. (Is Morphine Obsolete?)* §Robin Polt

- ¥ 16th Biannual Meeting of the American Peptide Society. June 1999, Minneapolis, MN. *Practical Glycopeptide Analgesics: Blood-Brain Barrier Transport and Binding of Glycosylated Enkephalin Analogs.* §Robin Polt, Scott A. Mitchell, Caroline T. Kriss, Matt R. Pratt, Peg Davis, Richard D. Egleton, Heather Jones, Edward J. Bilsky, Thomas P. Davis, Frank Porecca, Henry I. Yamamura, and Victor J. Hruby

- 1999 Gordon Conference on Natural Products. 25—30 July 1999, New England College, Henniker, New Hampshire. *Use of Conformationally-Restricted Schiff Base Moieties as Stereochemical Control Elements.* §Robin Polt, Brian Dangel and Hossein Razavi

‡ 203rd National Meeting of the American Chemical Society. 7 April 1992, San Francisco, California *α–and β-O-Glycosides via Nucleophilic Activation by Hydrogen Bond Acceptors. New synthetic Methods for O-Linked Glycopeptides and Glycosphingolipids.* §Robin Polt, Lajos Szabò & Matt A. Peterson.

¥ 203rd National Meeting of the American Chemical Society. 10 April 1992, San Francisco, California. *Sequential Reduction-Alkylation of Chelating Esters. Threo-Amino Alcohols.* §Robin Polt, Lynn DeYoung & Matt Peterson

‡ 205th National Meeting of the American Chemical Society. 30 March 1993, Denver, Colorado. *α–and β–O-Glycosides and O-Linked Glycopeptides: Potent Enkephalin Analogues Capable of Crossing the Blood-Brain Barrier.* §R.L. Polt, L. Szabò, H. Yamamura, F. Porreca & V. Hruby

‡ 205th National Meeting of the American Chemical Society 31 March 1993, Denver, Colorado. *N-Diphenylmethylene-Protected Glycosyl Acceptors: β–Selective Glycosylation to Form Lactosyl-threo-Ceramides.* §M.A. Peterson & R.L. Polt

• Southeast Regional Meeting of the American Chemical Society 29 November 1995, The Peabody, Memphis, Tennessee. *Glycopeptide Drugs and the Blood-Brain Barrier.* §Robin Polt

‡ 213th National Meeting of the American Chemical Society. 13—17 April 1997, San Francisco, CA. *Conformation and Dynamics of Enkephalin Glycopeptide Analogs.* §Caroline Kriss, Robin Polt, Victor J. Hruby & Scott Mitchell

• 14th Rocky Mountain Regional Meeting of the American Chemical Society. 15—18 March 1998, University of Arizona, Tucson, Arizona. *Amino Acids as a Source of Chirality for Enantiomerically Pure Alkaloids.* §Robin Polt, Dalibor Sames, Hossein Razavi, Scott Mitchell, and Brian Dangel

‡ 217th Meeting of the American Chemical Society. 21—25 March 1999, Anaheim, CA. *Amino Acid-Derived Schiff Bases in the Synthesis of Glycosidase and Glycosyltransferase Inhibitors.* §Robin Polt, Hossein Razavi, and Scott Mitchell

‡ 217th Meeting of the American Chemical Society. 21—25 March 1999, Anaheim, CA. *Activation of Aziridines: Nucleophilic Ring Opening.* §Brian D. Dangel and Robin Polt.

¥ 217th Meeting of the American Chemical Society. 21—25 March 1999, Anaheim, CA. *The Synthesis and Blood-Brain Barrier Transport Properties of O-Glycopeptide Analogs of Enkephalin.* §Scott A. Mitchell, Matt R. Pratt, Victor J. Hruby, Robin Polt.

‡ 219th ACS National Meeting, San Francisco, CA, 26—30 March 2000 *Glycopeptide Analgesics: Morphinelike Enkephalins with Reduced Addiction Potential.* §Palian, Michael M.; Mitchell, Scott A.; Kriss, Carolyn T.; Bilsky, Edward J.; Jones, Heather; Elmagbari, Nura O.; Egleton, Richard D.; Yamamura, Henry I.; Davis, Peg; Hruby, Victor J.; Polt, Robin.

‡ 219th Meeting of the American Chemical Society, 26—30 March 2000, San Francisco, CA. *New Polymeric Support For Solid-Phase Organic Synthesis: Formation and Cleavage of Aziridines and Transition-Metal Complexes Derived from O'Donnell's Schiff Bases.* §Dangel, Brian D.; Polt, Robin.

- *Development of Opioid Glycopeptides as Novel Analgesic Agents,* (sponsored by the 76th Annual Meeting of the Southwestern and Rocky Mountain Division of the American Association for the Advancement of Science), 9-12 April 2000, Las Cruces, NM. *O-linked Glycopeptide Enkephalin Analogs: Synthesis, Conformation and Binding.* [§]Robin Polt, Mike Palian, Peg Davis, Henry I. Yamamura, Thomas P. Davis, Frank Porreca, Richard Egleton and Edward J. Bilsky

- *Asymmetric Synthesis for the 21st Century* (sponsored by the 32nd Great Lakes Regional Meeting of the American Chemical Society) 4-6 June 2000, Fargo, ND. *Porphyrin Mimics Provide Useful Catalysts and Interesting Materials.* §Robin Polt and Brian D. Dangel

- *Workshop on DoD Sponsored Parkinson's Related Research* 22-34 March 2001, Potomac, MD, *Enzyme Inhibitors of Cell-Surface Carbohydrates: Insects as Model Systems for Neuronal Development and Repair Mechanisms.* §Robin Polt

- *2001 Gordon Conference on Natural Products* 29 July-3 August 2001, Tilton School, Tilton, NH. *Micrometalloenzymes. Use of Bifurcated Dipeptides as Ligands for Transition Metal Mediated Catalysis.* §Robin Polt and Brian D. Dangel

- *225th Meeting of the American Chemical Society* 23-27 March 2003, New Orleans, LA. *Glycopeptide Analogues Adopt Rigid Conformations in the Presence of SDS Micelles* §Robin Polt and Michael M. Palian

- *2003 Gordon Conference on Carbohydrates* 22—26 June 2003, Tilton School, Tilton, NH. *Glycopeptide Interactions with Membranes: Rationale for BBB Transport and Analgesia of Glycosylated Enkephalins* §Robin Polt

Regional/Local/Industrial

- Indiana University-Purdue University Organic Colloquium. 24 February 1993, Indianapolis, Indiana. *Amino Acid Schiff Bases: Versatile Synthetic Intermediates.* §Robin Polt

- University of Delaware Organic Symposium. 3 March 1993, Newark, Delaware. *Crossing the Blood-Brain Barrier.* §Robin Polt, Lajos Szabò, H. Yamamura, F. Porreca & V. Hruby

- Utah State University, Logan and
  University of Utah, Salt Lake City
  13 - 14 October 1993, Utah. *Synthesis and Biological Activity of Cell-Surface Carbohydrates.* §Robin Polt

- Columbia University Organic Colloquium. 7 September 1995, Columbia University, NYC, NY. *Schiff Bases in Organic Synthesis.* §Robin Polt

- Colorado State University Organic Colloquium. 24 September 1995, Colorado State University, Fort Collins, CO. *Synthesis of Amino Sugars and Aza-Sugars from Amino Acids.* §Robin Polt

- New Mexico State University Chemistry Department Colloquium.

18 January 1996, New Mexico State University, Las Cruces, NM.
Synthesis of Glycopeptides and Glycolipids [§]Robin Polt

- The Upjohn Company Seminar Series. 23 April 1992, Kalamazoo, Michigan. *New Synthetic Methods for Stereoselective Glycosylation of Serine: O-Linked Glycopeptides, Glycosphingolipids, and Glycosyl-Enkephalin Analogues.* §Robin Polt, Lajos Szabò & Matt A. Peterson

- Fort Lewis College Organic Symposium. 9 November 1990, Durango, Colorado, *Tandem C-C/C-O Bond Formation via Schiff Base Complexes: Sphingosines and Glycopeptides.* §Robin Polt, Yushun Li, Matt Peterson, Lajos Szabò & Thusitha Wijayaratne

- Oxford GlycoSystems Chemistry Division Seminar. 18 September 1995, Oxford GlycoSystems, Inc., Oxford, UK. *Synthesis of Amino Sugars and Aza-Sugars from Amino Acids* §Robin Polt

- University of Colorado Organic Division Seminar Series. 25 September 1995, University of Colorado, Boulder, CO. *Synthesis of Glycopeptides and Glycolipids* §Robin Polt

- Rohm & Haas Research Laboratories. 20 March 1998, Spring House, PA. *Synthesis of Amino Sugars, Aza-Sugars & Alkaloids from Amino Acids.* §Robin Polt

- Biosphere 2 (Columbia University West). 23 March 2000, Oracle, AZ. *Amino Acids in Organic Synthesis: The Conservation, Addition and Multiplication of Chirality.* §Robin Polt

- University of California, Irvine. 6 December 2000, Irvine, CA. *O'Donnell's Schiff Bases in Organic Synthesis.* §Robin Polt

- *Abbott Lecture Series.* Montana State University. 1 March 2002, Bozeman, MT. *Is Morphine Obsolete? Glycopeptide Enkephalins as Non-Toxic Alternatives to Morphine.* §Robin Polt

- Neose Technologies, Inc. 14 June 2002, Horsham, PA. *Glycopeptide Analgesics.* §Robin Polt

- John Carroll University, 29 September 2004, University Heights, OH Case Western Reserve University, 30 September 2004, Cleveland, OH. *Sugar-Coated Neuro-Peptides that Sneak Through the Blood-Brain Barrier: Designer Drug Substitutes for Morphine.* §Robin Polt

- Northeastern University, 23 February 2005, Boston, MA. *"Membrane-Mediated Glycopeptide Transport: Penetration of the Blood-Brain Barrier"* §Robin Polt

Posters (selected)

‡ 4th Symposium on the Latest Trends in Organic Synthesis. 15 - 17 October 1990, Blacksburg, Virginia.*Anti-Viral Dexoy-C-Nucleosides..* Thusitha Wijayaratne & §Robin Polt

‡ 9th Biennial Carl S. Marvel Symposium — Organic Synthesis. 11—13 March 1991, Tucson, Arizona. *Glycosphingolipids via Tandem C-C/C-O Bond Formation.* *Matt A. Peterson & Robin Polt

‡ 9th Biennial Carl S. Marvel Symposium — Organic Synthesis 11 - 13 March 1991, Tucson, Arizona. *New Synthetic Methodology for 2-Deoxy-C-Nucleoside Analogues..* §Thusitha Wijayaratne & Robin Polt

‡ 1991 Gordon Conference on Natural Products. 25 - 29 July 1991, New Hampton, New Hampshire. *Glycosphingolipids via Aluminoxy-Acetals..* §Robin Polt, Matt Peterson & Lynn DeYoung

‡ 1992 Natural Products Gordon Conference. 20 - 24 July 1992, New Hampton, New Hampshire. *Synthetic Methods for Glycosphingolipids and Glycopeptides.* (Poster selected for short talk.) §Robin Polt, Matt A. Peterson & Lajos Szabò

¥ 1992 Natural Products Gordon Conference. 20 - 24 July 1992, New Hampton, New Hampshire. *Lewis Acid-Catalyzed reactions of Mono-Silyl Acetals..* §Robin Polt, Lynn DeYoung, Yunqi Liu & Dalibor Sames

‡ 12th International Symposium on Glycoconjugates (GLYCO XII). 15—20 August 1993, Krakòw, Poland. *Aluminoxy-Acetals from α-Amino Esters: Chirality Transfer via Sequential Addition of Hydride and C-Nucleophiles.* §Robin Polt and Matt A. Peterson

‡ XVIIth International Carbohydrate Symposium. 17 - 22 July 1994, Ottawa, Canada. *General Glycosidation Methods for α– or β–O-Glycopeptides Which Cross the Blood-Brain Barrier. A New Class of "Designer Drugs."* §Lajos Szabò, Frank Porreca, Victor J. Hruby and Robin Polt

‡ XIIIth International Symposium on Glycoconjugates. 20 - 26 August 1995, Seattle, WA. *An Asymmetric Synthesis of L-Azafucose and Azafucosylceramide from L-Alanine.* §Dalibor Sames and Robin Polt

‡ National Academy of Sciences' Colloquium: "Molecular Kinesis in Cellular Function and Plasticity." 7 - 9 December 2000, Beckman Center, Irvine, CA. *D-threo-PDMP and Structural Analogs Alter GSL Expression in Manduca sexta and Reduce Neurite Extension in Explants.* §Robin Polt, Lynne Oland, Chris Biland, James B. Glick, Bennett Novak, Jacob Slavish, Will H. Taylor, Kathy McGovern and John Hildebrand

‡ indicates contributed paper
¶ indicates reviewing the state of the field, etc.
• indicates invited manuscript
§ indicates principal author
* indicates work done as a graduate student
** indicates work done as an undergraduate student
¥ indicates contribution by an undergraduate research participant
† indicates original research - not reported elsewhere

Grants and Contracts

Funded Grants - R. Polt as P.I.

Synthesis and Characterization of Chelating Polymers.
American Chemical Society—Petroleum Research Fund, Type G
$18,000 (1989—1991)

Synthesis of Glycosidase Inhibitors from Simple Sugars and Anionic Glycine Synthons.
National Institutes of Health—Biomedical Research Support Grant
$5,000 ($4,814 requested) (1989—1990)

Total Synthesis of Gangliosides: GM3
American Cancer Society—Institutional Cancer Research Grant
$9,525 (1989—1990)

Aluminoxy-Acetals: New Applications for Alkaloid Synthesis.
University of Arizona—Materials Characterization Program
$4,000 (1991—1992)

Cell-Surface Glycoconjugates.
National Science Foundation Grant
$195,000 (1992— 1995)

Construction of Polysaccharide Libraries to Probe Molecular Recognition.
Selectide Corporation, Tucson, AZ
$64,000 (1992—1993)

The Synthesis and Characterization of Chelating Polymers.
DuPont Discretionary Funds
$3,334 (1993)

10th Biennial Carl S. Marvel Symposium
Research Corporation
$1,000 (1993)

Crossing the Blood-Brain Barrier. Glycosylation of Neuro-Active Peptides to Produce Physiologically Active Drugs.
Arizona Disease Control Research Commission
$63,750 (1993—1996)

Ethocyn— Synthetic Methods.
Chantal Pharmaceutical Corporation, Los Angeles, CA
$44,000 (1995—1996)

Cell-Surface Glycoconjugates II.
National Science Foundation Grant

$279,000 (1995— 1998)

New Ligand Systems for Transition Metal Binding
University of Arizona—Materials Characterization Program
$3,800 (1997)

14th Rocky Mountain Regional A.C.S. Meeting
Research Corporation
$2,500 (1997)

Micro-Metallo Enzymes: Synthetic Methods and Characterization.
University of Arizona—Materials Characterization Program
$2,750 (1998)

Gifts for the Support of the Polt Group
Matreya, Inc., Pleasant Gap, PA
$18,478 (1998-2003)

Solid-Phase Supports for Combinatorial Catalyst Discovery.
University of Arizona—Materials Characterization Program
$1,200 (1999)

Technology Partnership Grants and Student Achievement Award
GenCorp Foundation, Inc.
$8,500 (1999)

Synthesis and Methodology for New Glycosyltransferase Inhibitors
Arizona Disease Control Research Corporation
$111,699 (1999-2001)

Enzyme Inhibitors of Cell-Surface Carbohydrates: Insects as Model Systems for Neuronal Development and Repair Mechanisms
$575,485 U.S. Army (1999-2004)

Enkephalin Glycopeptides Penetrate the Blood-Brain Barrier: Non-Toxic Alternatives to Morphine in Combat Casualty Care. N00014-02-1-0471
$1,251,229 Office of Naval Research (2002-2005)

A Request for Funding to Support the cGMP Manufacture of Glycosylated Enkephalins and Pre-Clinical Evaluation
$410,340 (2004) –(FY04 "ramp" invited by Program Manager)

Non-Toxic Glycopeptide Analgesics for Combat Casualty Care. N00014-05-1-0807
$1,541,457 Office of Naval Research, Combat Casualty Care Program (2006-08)

Cell Surface Glycoconjugates III
National Science Foundation Grant

$351,000 (2006-2009) ($543,590 requested.)

Non-Toxic Glycopeptide Analgesics for Combat Casualty Care. Supplement.
N00014-05-1-0807
$218,500 ONR, Combat Casualty Care Program (2006)

$ 5,183,565 total funding for the Polt Group

Funded Grants - R. Polt as Contributor

X-Ray Structure Determination System.
National Institutes of Health—Shared Instrumentation Program
$230,000 (1990)

New Modalities for the Treatment of Drug Abuse
National Institute for Drug Abuse (1993—2002)
Polt Group Share ~$180,000 (V.J. Hruby, PI)

Research Experiences for Undergraduate Women in Materials Chemictry.
National Science Foundation—Research Experience for Undergraduates
$120,000 (1992—1995)

A Fourier Transform NMR Spectrometer for Undergraduate Use.
National Science Foundation
$100,000 (1993)

Upgrade and Acquisition of NMR Instrumentation.
National Science Foundation
$173,000 (1993)

Proposal for a New NMR Console.
National Science Foundation
$155,000 (1996)

An Astronomical Search for the Essential Ingredients of Life: Placing Our Habitable System in Context
NASA (17-99-1-9539)
$5,957,147 (2003—2006)
(22 collaborators in total: 17 – Arizona, 3 - NOAO, 1 - UC Berkeley, 1 - Ohio State, ~$60,000 in direct costs to Polt Lab)

Upgrade of Variable Frequency Pulsed EPR Facility
National Institutes of Health
$204,500 (2005)

Pending

Amphipathic Glycopeptide Hormones and Biological Membranes
National Science Foundation (CHE Organic Dynamics)
$539,583 (2006—2008) pending

Biousian Glyconeuropeptide Amphipaths Penetrate the BBB
National Institutes of Health
$2,805,387 (2005—2010) pending

Drugs for the Brain from the Brain: Endogenous Neuropeptides for Analgesia and Depression
Arizona Disease Control Research Commission (ADCRC)
$450,000 (2006—2008) pending

Invention Disclosures

Method for Making Amino Acid Glycosides and Glycopeptides.
Robin Polt (Invention Disclosure **UA1258**)
Patent Granted 28 November **1995**, US #5,470,949
Patent Granted 16 June **1998**, US #5,767,254

Method for Making Glycosphingolipids and Related Analogs.
Robin Polt (Invention Disclosure **UA1249**)

O-Glycosylation of Biologically Active Peptides for Crossing the Blood-Brain Barrier.
Robin Polt, Victor J. Hruby, Frank Porreca & Lajos Szabò
(Invention Disclosure **UA1253**)

A Chiral Ligation System for Main Group and Transition Metal Catalysis
Robin Polt (Invention Disclosure **UA1562**)
Patent Granted 9 November **1999**, US #5,981,783

A Method for the Synthesis of threo-Dihydrosphingosine and Related Glycosphingolipid Processing Inhibitors
Robin Polt (Invention Disclosure **UA1750**)

Resin-Bound Diphenylketimine
Robin Polt (Invention Disclosure **UA 2000-042**)

Multiple Glycosylation of Enkephalin Analogues Leads to Enhanced CNS Delivery after Sub-Cutaneous Administration
Robin Polt (Provisional Patent filed February 25, 2003. Serial No. 60/449,989)

Statement of Objectives on Teaching, Research, and Service/Outreach

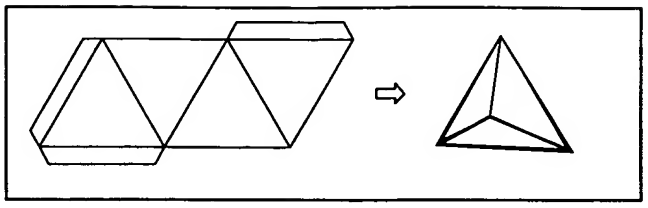
Philosophy. I view the University's Mission as a learning process which spans a continuum, which may be divided into 5 (not two) levels of learning: lower division, upper division, master's level, doctoral and post-doctoral education. In the global economy that is emerging, what a student is capable of learning in the future is just as important as how much that student knows when he or she graduates. The primary mission of a research oriented university should be on *training students to do research,* not simply on research as an end in itself. As such, my own approach to research is a highly integrative one in which undergraduate research is integrated into our goals in a thoughtful way.

Lower Division Teaching (a.k.a. Large Undergraduate Lectures). Chemistry represents much more for me than a collection of fact & theory, a technology, or even an art. Although it is all of these, it also provides both an intellectual and metaphorical framework for continued learning understanding life. For the initial introductory "O-Chem" lecture, I invoke the imagery of popular music: *"We are stardust. We are golden. We are billion-year-old carbon..."* Since carbon is the basis for all life as we know it, illustrative examples of organic chemistry which are familiar to most of the students are presented to the students. I have learned that an important task in lecturing to large heterogeneous groups is to both interest and entertain the students, otherwise they become bored, and ultimately stop trying to learn, or even attend class. I take pride in the fact that attendance at my lectures is excellent. It is also important to be honest with the students, and to be firm with respect to the conduct of the course, to scientific rigor, and to scholarly principles. To this end, and to the consternation of my students and graders alike, I do not give multiple-choice exams. Likewise, I have never scheduled makeup tests, or given "incompletes" except under the most compelling of circumstances.

I have always tried to maintain the course focus on the student and the learning process, and not on *the material.* I spend a considerable amount of time with the students outside the lecture hall in tutoring and advising. These interactions occur in large groups (20—60) during "help sessions," in small groups (3—6) at the hallway blackboard outside my office after class, or in one-on-one situations in my office or laboratory. A number of my 1st and 2nd semester students have asked me for recommendations to various programs and professional schools, for career counseling, and for advice. As an educator I regard this sort of "mentoring" as a very important and critical aspect of my work.

When I first started teaching I worried a great deal about the presentation of *the material.* By using a "construction approach," I found that I could incorporate the third dimension (*e.g.* stereochemistry) into "O-Chem" from the very first day, by having each students cut and tape together several small paper tetrahedra, one of which would be

decorated, signed, and turned in for "credit." The main purpose of this apparently trivial construction was to illustrate the tetrahedral nature of carbon, but it also served to reassure the anxious pre-med student that the material was comprehensible. Since a student's name was written on each tetrahedon, I also used them to call on students to answer questions. I would subsequently use their tetrahedra to illustrate such concepts as hybridization, bonding, and chirality in carbon-based molecules. Of course, the class eventually graduates to Darling Models®, and far more complex issues are addressed in the second semester.



My approach at the undergraduate level has evolved from one focused on the material and its presentation to a more interactive one, in which the student (even in a 250-seat auditorium) is a participant. Molecules and functional groups become actors in molecular dramas (reactions), and I try to assume the role of narrator to draw the students into the action, which is at times comedy, at times Shakespeare, and sometimes classical Greek tragedy. In classes of this size, there is an element of theater involved, and students are far more likely to remember *"...the lonely pair of electrons* (:NH_3) *looking across a crowded dance floor* (solvent) *for an empty orbital* (BF_3)..." and then apply that imagery to the more abstract molecular orbital treatment that follows.

While my own physical and synthetic roots are apparent in my treatment of introductory organic chemistry, many of the examples used as "actors" are molecules of biological importance: metabolites, neurotransmitters, and natural products. The student learns the structures and importance of pentoses, hexoses, amino acids and nucleosides. Many students have remarked that they wish they had taken my course as a true sophomore, rather than putting off the dreaded "O-Chem" until their Junior or Senior year. Nothing pains me more than the biochemist or medical student who thinks of chemistry as nothing more than a collection of letters and symbols, and when I can convince a bright young student to follow a career in science, rather than clinical medicine, I feel like I have been most successful.

Upper Division Teaching. At the more senior undergraduate level, finer laboratory technique and more complex theory is introduced, and the exercises become more demanding in terms of organizational skills and independence. In the course I have developed, the student is challenged to create his or her own intellectual and organizational framework, rather than being tested in a highly structured environment.

For five consecutive years I taught an advanced organic laboratory course for Senior chemistry majors (generally 15-20 students), which was an "organic preps" course when I inherited it. I replaced the hodge-podge of preparations with two experiments designed to

illustrate the fundamental nature of chirality, diastereoisomerism and enantioselective synthesis. The first brief experiment involved the classical resolution of α-phenethylamine *via* the formation of a diastereomeric salt with tartaric acid. The students were then required to use chiral lanthanides and NMR to determine the enantiomeric excess of their products, and to report their results as a scientific communication (*e.g. J. Am. Chem. Soc.*).

The second experiment allows the students to "take ownership" of a research project, and each student must produce an optically pure amino acid from glycine and a chiral phase-transfer catalyst. By providing each student with a different alkylating agent, I can be assured that they will *work independently* in one sense, but by providing a methodological framework in which to work, I can also be assured that they will *work together* to understand the chemical concepts behind the experiment. Thus, given a precisely defined synthetic target, yet only loosely defined methods (*i.e.* a finite, yet large number of solutions, relative to 16 weeks), the students are asked to research the problem in the library, and propose solutions, which are then examined in the laboratory. More often than not, their initial experiments fail, and modifications in their experimental conditions are required before a 2nd or 3rd attempt is made— as in real life. The weekly lecture focuses on theory and technique, initially, but towards the end of the course, the lectures focus on amino acids as components of antibiotics— penicillin and vancomycin, and the bacterial cell wall. Thus, by the end of the course, the student is ready to present their work in a "full paper" format, including a discussion of the importance of non-proteogenic amino acids. The students enjoy this course because they are encouraged to express their individuality in their work, and to demonstrate their leadership potential.

Research Objectives. Every endeavor has tactical as well as strategic objectives. Thus far, we have managed to demonstrate that some rather simple chemical concepts can be used to provide solutions to a large number of problems, chemical and otherwise. Since it is not possible for us to approach the whole range of potential synthetic problems available to us, we have chosen to let our strategic interests define our problems (Think globally, act locally?). Since strategy is ultimately limited by the available tactics, let me first explain our tactical goals. Tactics, for our research group, means new synthetic methods— the exploration of chemical reactivity, and the exploitation of this reactivity for the stereoselective construction of carbon-carbon, carbon-oxygen, and carbon-nitrogen bonds.

Synthetic Methods. My first Ph.D. student, **Matt Peterson** (now Asst. Prof. at Brigham Young University), was able to generate functional α-amino aldehyde equivalents *via* the generation of aluminoxy-acetals by reduction of Schiff base-protected α-amino esters with $iBu_2AlH \bullet iBu_3Al$. Matt added various nucleophiles (RMgX, RLi) to the aluminoxy-acetals to produce substituted *threo*-β-amino alcohols with high selectivity. This approach has since

allowed subsequent students **Dalibor Sames** (now Asst. Prof. at Columbia University), **Hossein Razavi** (now a Post-Doc. with Prof. Jeff Kelly at Scripps), **Scott A. Mitchell** (now a chemist at Neurogen, Inc.), and **Brian Oates** (master's student at Merck & Co.) to synthesize a number of glycosidase and glycosyltransferase inhibitors from amino acid Schiff bases. These methods have been used to produce homologues of D- and L-threonine for use in the synthesis of pharmacologically active "sphingopeptides" and "glycosphingopeptides" by 3rd-year student **Michael M. Palian**, and should lead to the total synthesis of (+)-lycoricidine by 1st-year student **Mark Lefever**.

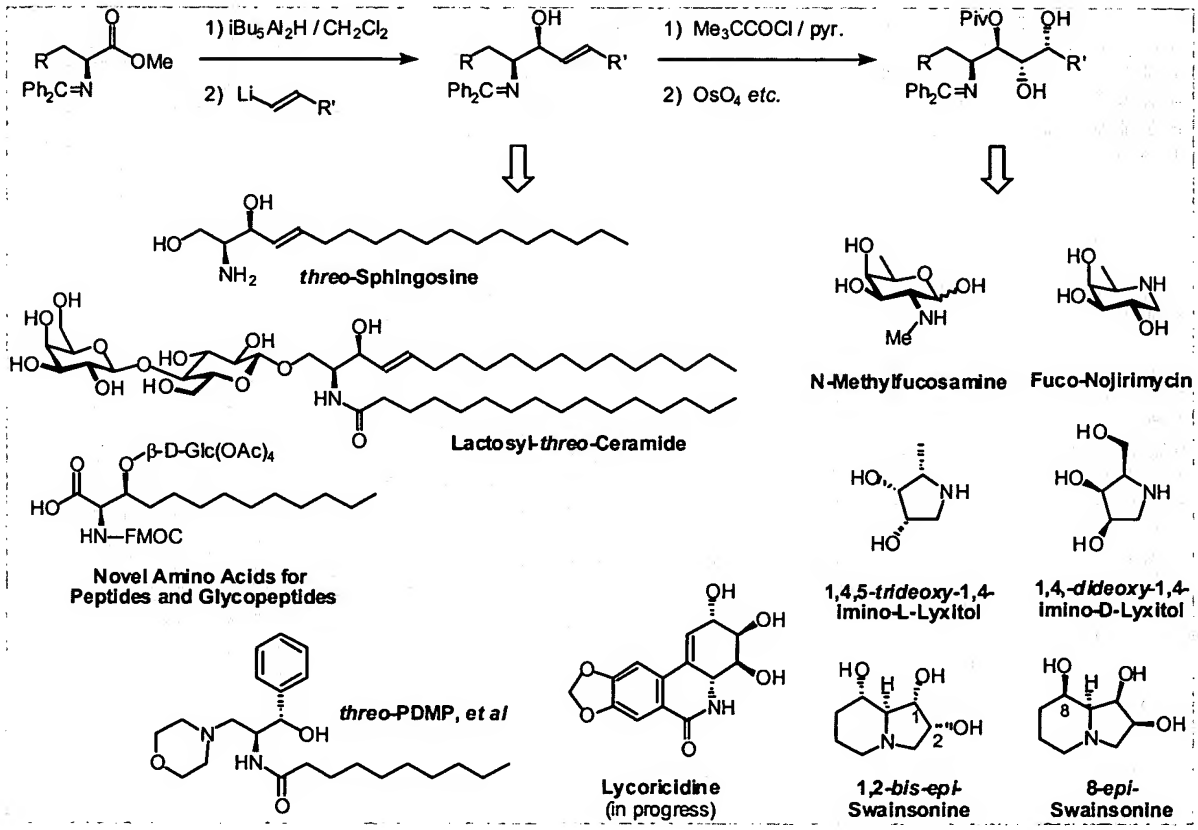
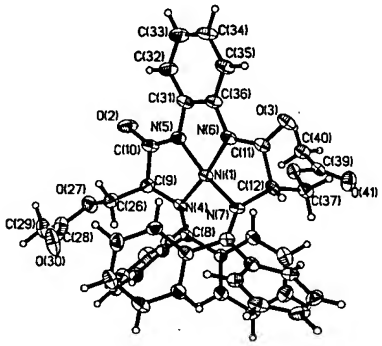


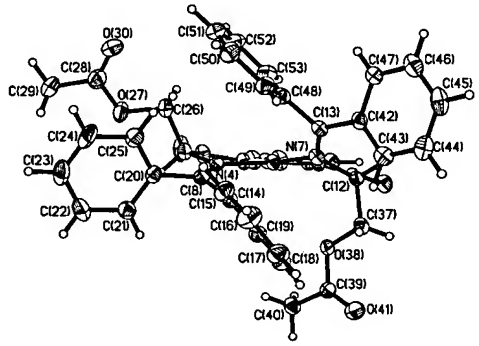
Figure 1. Synthetic Methodology Developed in the Polt Group.

We feel that the reductive alkylation chemistry has now been sufficiently "showcased" to demonstrate the synthetic utility of the method, and have now moved on to less obvious applications of the benzophenone imine as a metal-binding moiety. In addition to using the complexing ability of the imine ($Ar_2C{=}N{:} \rightarrow Li^+$ or Mg^{++}) to effect Cram-type *diastereoselective* alkylation processes (*e.g. chirality addition*), we have expanded our interest to include the use of amino acid-derived transition metal complexes (**Figure 2**) for *enantioselective* catalysis (*e.g. chirality multiplication*). These efforts, spearheaded by **Brian Dangel** (who graduated recently to *Post-Doc with former student **Dalibor Sames** at

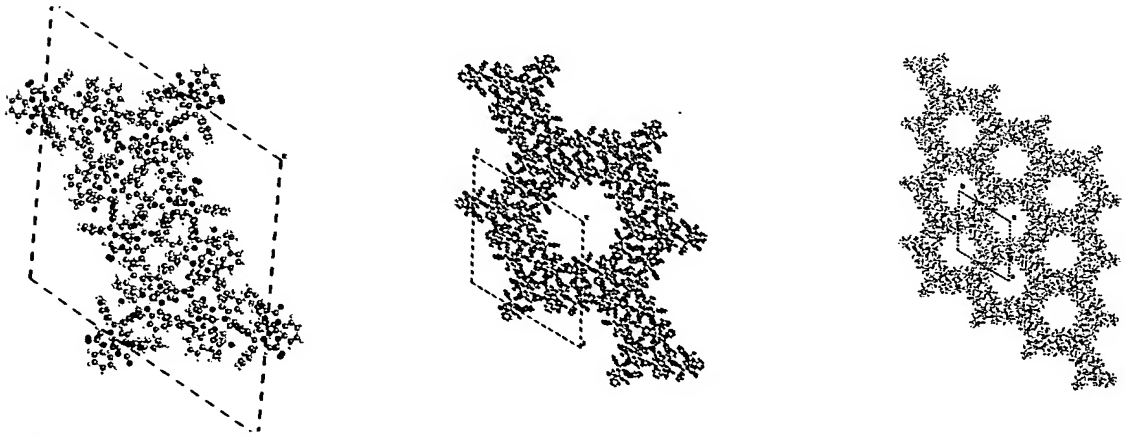
* It is noteworthy that Brian turned down a very attractive offer from Dow Chemical in order to further his education by working on a project involving the total synthesis of a natural product.

Columbia University), have led to the design and use of enzyme-inspired "micro-metalloenzymes," as well solid-phase methods which should allow us to optimize ligand selection and discover new catalysts through parallel synthesis and screening approaches (**Figure 3**). One could regard this process as a technology-based "chemical evolution" of our complexes. These efforts have now been picked up by 1st-year students **Brian Kelly** and **Baskhar Tadikonda**, and I feel there is a wealth of useful chemistry here yet to be discovered. *The degree to which combi-chem has divided the synthetic community is surprising to me. Many of my colleagues have either flung themselves headlong into combi-chem with abandon, or else shunned this technology entirely.* Choosing the middle path, we have chosen simply to regard "combi-chem" as a new tool that allows us to run many reactions simultaneously, so as to gather information that would be practically impossible using more classical techniques (*e.g.* test <u>all</u> the 1st-row transition metals to see if they will catalyze an enantioselective Kharash-Sosnovsky reaction).





Top View of Ni^{II}-(O-Ac-Ser)$_2$ Complex Side View



Ni^{II}-Ser$_2$ Complex Forms Stable "Honeycomb" Crystals with 20Å Channels. M.P. >220°C in Air!

Figure 2. Transition Metal Complexes Characterized by X-Ray Structural Analysis.

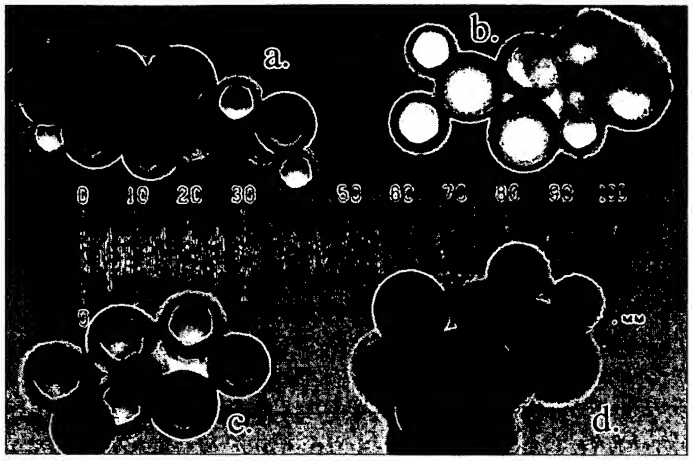


Figure 3. Transition Metal Complexes on Polystyrene Beads. a) Wang—Ar_2C=NH, b) Wang—L-Phe-L-Phe Ligand Only (no metal loading), c) Wang—L-Phe-L-Phe Ni^{II}, d) Wang—L-Phe-L-Phe Cu^{II}.

Glycobiology (Applications). Glycosylation methods which were explored early in my tenure at the U. of A. have undergone refinement, and are now being exploited for the synthesis of novel glycoconjugates and enzyme inhibitors. These compounds are now being evaluated in biological systems involving mice and rats (glycopeptide based analgesia), human cancer cell lines (metastasis inhibition), and insects (neuronal development). While these projects are collaborative, they are all synthesis-driven, and have required a large investment of time and energy on our part to understand the biology (pharmacology, neuroscience, cell biology, and medicine) and propose the appropriate experiments. We regard these applications (molecules) as examples of *"chemical semiotics"*— chemical signs which contain biological meaning. I also firmly believe that our research group, with our emphasis on both classical methods of chemical synthesis, as well as the development of new synthetic methods, is in a position to make substantial contributions to the emerging glycobiology of the 21st century.

In naturally occurring glycoproteins, glycopeptide hormones, and glycolipids the carbohydrate moieties control the intracellular trafficking and intercellular transport of the gene products, as well as inter- and intracellular signaling by glycosphingolipids *in vivo.* Clearly, there is much work to be done in the area of complex carbohydrates, and our synthetic skills will be needed to help unravel the bewildering array of polysaccharides which appear in living organisms. This emerging field of **glycobiology** may be regarded as a province complementary to classical molecular biology. Whereas molecular biology deals with the storage, retrieval, and evolution of biological information in DNA & RNA structures; glycobiology deals with biological information which is stored and expressed in the structural architecture of the cell itself, its membrane systems, and its associated complex carbohydrates. I firmly believe the present emphasis on genetic approaches to biological problems, as powerful as they are, needs to be balanced by a more inclusive

molecular biology— one which regards DNA as a molecule of central importance, but only one of many evolving chemical structures within a cell.

Initially, this work began with the development of several synthetic methodolgies by **Matt A. Peterson** (now an Assistant Professor at Brigham Young University, Logan, Utah), **Dr. Lajos Szabò** (now a chemist at S.I.D.D.Co., Tucson, AZ), and **Scott A. Mitchell**. Use of NMR, CD, and bioassays to relate the unambiguous synthetic constructs (structures) to molecular shape (conformations) and biological meaning (pharmacology & glycobiology) has been pursued by **Thusitha Wijayaratne** (now a lecturer at the University of Columbo, Sri Lanka), **Caroline Kriss** (now a Post-Doc at the University of Minnesota), and 4th-year **Michael M. Palian**.

I have high regard for my students, and while they receive a great deal of detailed direction early on in their careers, I never treat a student only as a pair of hands, rather as scientific colleagues. I expect each student to gain the skills necessary to do independent research, to propose new solutions and problems, and to be able to present his or her results both orally and in written form. I have found that this approach to graduate training scares off a number of graduate students who are not ready to accept responsibility (ownership) of their research project, but the ones who do take on the challenge seem to be capable of contributing to the scientific enterprise at every level. I am particularly proud of my women Ph.D.'s, who constitute 1/3rd of our graduates, who are of course our most important "chemical products."

Service/Outreach Objectives. These objectives are, by their very nature, defined by the needs of others. Reviewing papers and proposals, writing review articles, chairing sessions, and organizing symposia are all activities which I have done, and will continue to do in support of my scientific discipline. I have made contributions to successful federal grant applications for undergraduate training (*NSF—REU* program), for upgrading our nuclear magnetic resonance facility, and our X-ray structure determination facility.

I have been active in the Southern Arizona Section of the American Chemical Society, holding the offices of Treasurer, Secretary, and Chair-Elect. It was as Treasurer of ACS that I first became involved with the Marvel Symposium Series, a biennial symposium on organic chemistry, which I organized in 1993, which focused on Organic Synthesis and Methodology. In 1998 I organized a multi-track meeting, the Rocky Mountain Regional Meeting of the American Chemical Society. This meeting, which attracted over 400 paying participants, was the first regional meeting to be held at the University of Arizona.

I have arranged for a number of seminar speakers at very minimal or no cost to the Chemistry Department, both from academia, as well as pharmaceutical concerns such as Upjohn, Abbott, Merck, Searle, and Scherring—Plough. Some of our graduates have been placed as a result of these visits, and I think this is a very important duty for the faculty.

That is, we need to get out into the world, and bring the world into the Chemistry Department so that our students have an opportunity to interact with and ultimately work with a wide variety of professional chemists. A serious danger for Chemistry in the coming decades is that the *Discipline of Chemistry* may become lost within its enormous potential for new *chemical applications,* and fragment into a number of application-driven efforts. It is important that chemists "keep the flame alive," yet remain flexible in terms of new applications. In a recursive sense, this brings us back to my teaching objectives.

Teaching and Advising

Extent of Teaching

1995	Fall	CHEM-446 *Organic Preparations*	10 students
1996	Spring	CHEM-640 *Advanced Organic Synthesis*	14 students**
1996	Fall	CHEM-446 *Organic Preparations*	11 students
1997	Spring	CHEM-646 *Advanced Organic Chemistry* *(Topic: Carbohydrates— Chemistry, Biology & Medical Aspects)*	9 students
1997	Fall	CHEM-241A *Organic Chemistry I*	158 students*
1998	Spring	CHEM-241B *Organic Chemistry II*	76 students*
1998	Fall	CHEM-540 *Organic Syntheses*	16 students**
1999	Spring	CHEM-241B *Organic Chemistry II*	191 students*
1999	Fall	CHEM-540 *Organic Syntheses*	24 students**
2000	Spring	CHEM-546 *Advanced Organic Chemistry* *(Topic: Carbohydrates— Chemistry, Biology & Medical Aspects*	9 students**
2000	Fall	CHEM-446 *Organic Preparations*	14 students
2001	Spring	CHEM-540 *Organic Syntheses*	17 students
2001	Fall	CHEM-446 *Organic Preparations*	10 students

* Data from "Instructor's T.C.E. Report" included:

	Fall 1997	Spring 1998	Spring 1999
1. Overall rating of instructor's effectiveness	3.8	3.9	3.7
2. Comparison of overall rating of instructor's effectiveness	3.3	3.7	3.4
3. Overall, how much did student learn (self-report)	3.5	3.7	3.6
4. Overall rating of this course-section	3.2	3.6	3.2
5. The textbook(s) and readings used in this course	3.2	3.4	3.9
6. The usefulness of outside assignments	3.8	3.9	3.7
7. The usefulness of the in-class activities	4.0	4.1	3.8
8. Student treated with respect in class	4.5	4.3	4.2
9. The difficulty level of the course activities & materials	4.4	4.7	4.5

** Data from "AXΣ Course Evaluation Form" included:

See appendix material.

Teaching Awards and Grants

Who's Who Among America's Teachers (multiple year honoree)

Individual Student Contact

Mentoring

Undergraduate

Student	Placement
Chris Baer (UBRP)	Dental School University of North Carolina
Jonathan Baines	*unknown*
Josh Bagnato	Graduate Chemistry Program University of Utah
Becky Barner (REU)	*unknown*
Jason Chruma (Goldwater Fellow, Outstanding Junior Chemistry Major, Outstanding Senior, NSF Pre-Doctoral Fellow)	Ph.D., University of Pennsylvania Post-Doc, Columbia University
Michael Clarke (UBRP, Outstanding Senior)	Graduate Chemistry Program, Stanford University
Walter Cook	*unknown*
Lynn DeYoung (UBRP)	M.D.-Ph.D. Program University of Nebraska
Paul Durand	*unknown*
Donna Friel (McNair Fellow)	*B.S. in Progress at the University of Arizona*
David Goldstrom	*unknown*
Betsy Gross (REU)	M.D. Program University of Connecticut
Richard Grossman (UBRP)	U.S. Navy
Patti Jenkins	*unknown*
Courtney Langdon	M.D. Program University of Arizona
Beth Melnik	*unknown*
Theresa O'Sullivan	Staff Scientist Pharmacia, Kalamazoo, MI
Krzysztof Pietrzak	Staff Scientist Gor-Tex, Flagstaff, AZ
Matt Pratt (DARE, Outstanding Biochemistry Senior)	Graduate Chemistry Program, U.C. Berkeley
Joel Renick	*unknown*
Jamie Ropacki	Staff Scientist Baer Pharmaceuticals, Elkhart, IN
Regina Ross (DARE, Morterboard)	M.D. Program University of Arizona
Will Taylor	Ph.D. Program (Biochemistry) University of Arizona
Andreas Throuvalas	*unknown*
Jennifer Treiberg (REU)	Staff Scientist

	Pharmacia, Kalamazoo, MI
Wesley Vaughn	*unknown*
William Watts	*unknown*
Lois Chun	*unknown*

Graduate

Student	Placement
Colby Caldwell (MA 1997)	Ph.D. Program in Medicinal Chemistry University of Arizona
Brian Dangel (Ph.D. 2000)	Post-Doctoral Study Chemistry Department Columbia University, New York City, NY
James Glick	*Ph.D. in Progress at the University of Arizona*
Alan Iwamoto	*unknown*
David Heddens (M.A. 1996)	*unknown*
Elaine Kellogg (M.A. 1991)	Ph.D. Program Chemistry Department Iowa State University, Ames, IW
Brian Kelly (Mid-Career Fellow)	*Ph.D. in Progress at the University of Arizona*
Caroline Kriss (Ph.D. 1999) (Mid-Career Fellow)	Post-Doctoral Study Chemistry Department University of Minnesota, Minneapolis, MN
Mark Lefever (M.A. in progress)	Staff Scientist Abbott Labs, Casa Grande, AZ
Scott Mitchell (Ph.D. 1999) (Mid-Career Fellow, Marvel Award Nominee)	Senior Chemist Neurogen Corporation, New Haven, CT
Sean Moore (M.A. 1994)	*unknown*
Bryan Oates (MA 1997)	Staff Scientist Merck Discovery, Princeton, NJ
Michael Palian (Ph.D. 2002) (A.R.C.S. Foundation Fellow)	*Ph.D. in Progress at the University of Arizona*
Matt Peterson (Ph.D. 1992) (Marvel Award Nominee)	Associate Professor Brigham Young University, Provo, UT
Hossein Razavi (Ph.D. 1999) (Mid-Career Fellow, Graduate College Dean's Fellowship)	Post-Doctoral Study Chemistry Department Scripps Institute, La Jolla, CA
Dalibor Sames (Ph.D. 1996) (Mid-Career Fellow, Teaching Excellence Award, Marvel Award)	Associate Professor Columbia University, New York City, NY
Jake Slavish	*Ph.D. in Progress at the University of Arizona*
Jennifer Smith (MS in progress)	Staff Scientist S.I.D.D.Co., Tucson, AZ
Bhaskar Tadikonda (Mid-Career Fellow)	*Ph.D. in Progress at the University of Arizona*
Thusitha Wijayaratne (Ph.D. 1993)	Lecturer University of Columbo, Columbo, Sri Lanka

Post-Doctoral

Student	Placement
Yushun Li	Staff Scientist Synthetic Core Facility of the University of Arizona Center for Toxicology
Lajos Szabò	Chemisty S.I.D.D.Co., Tucson, AZ
Jan Ramza	Staff Scientist Pharmaceutical Research Institute, Warsaw, Poland
Thusitha Abeytunga (*nee* Wijayaratne)	Senior Lecturer University of Columbo, Columbo, Sri Lanka
Dhanasekaran Muthu	Doshisha Women's University Kyotanabe-Shi, Kyoto
Leif Abrell	Work in progress

Participation in Honors Programs

Undergraduate Biology Research Program (UBRP)
DuPont-Arizona Research Experience (DARE)

Independent Studies

Donna Friel (McNair Fellow)
New Methods for the Synthesis of GSL Processing Enzyme Inhibitors

Independent studies directed in the last 5 years

Jason Chruma (Honors Thesis in Chemistry 1997)
Active Protection of Amino Acids

Regina Elizabeth Ross (Honors Thesis in Molecular and Cellular Biology 2001)
Amino Acid Derived Ligands for Synthesis

Will Taylor (Honors Thesis in Biochemistry 2001)
Isolation and Identification of Glycosphingolipids from Manduca sexta

Dissertations in Progress

Brian Kelly (6th year)
Charles M. Keyari (5th year)
Larisa Yeomans (4th year)
Shang-U Kim (4th year)
Alex Fosse (3rd year)
Yingxue Li (2nd year)

Dissertations

Matt A. Peterson *Stereoselective Synthesis of beta-Amino Alcohols and Glycosphingolipids: N-Diphenylmethylene Protection for Tandem C-C/C-O Bond Formation (1992)*

Thusitha Wijayaratne *Part 1: 2-Deoxy-C-Glycofuranosides from D-Glucose Part 2: An Approach to N-Acetylneuraminic Acid from Carbohydrate Precursors (1993)*

Dalibor Sames *Stereoselective Oxygenation of a Double Bond: Design and Synthesis of Azasugar Inhibitors of Glycoconjugate Processing Enzymes (1996)*

Caroline Kriss *Conformational Analysis of O-Linked Glycopeptides Related to Enkephalin and Nuclear Pore Proteins (1999)*

Hossein Rasavi *Amino Acid Schiff Base Methodology for the Synthesis of Glycosidase Inhibitors: Polyhydroxylated Pyrrolidines and Indolizidines (1999)*

Scott A. Mitchell *O-Glycopeptide Analogues of Enkephalin: FMOC-Amino Acid Glycoside Synthesis, Solid-Phase Glycopeptide Synthesis and Optimizations, and Pharmacology (1999)*

Brian D. Dangel *Efforts Toward the Development of a Universal Catalyst System: Transition Metal Complexes Derived from O-Donnell's Schiff Base Amino Acids (2000)*

Michael M. Palian *Glycopeptide Enkephalin Analogs: Design, Synthesis, Biophysical and Pharmacological Evaluation of Potent Analgesics with Reduced Side-Effects (2002)*

Jake Slavish *Synthesis and Biological Evaluation of Analogues of a Glycosyltransferase Inhibitor (2004)*

Udaya Bhaskar Tadikonda *Design, Synthesis and Applications of Tetradentate Transition Metal Complexes Towards Asymmetric Alkylations (2005)*

Service on Dissertation Committees other than as an advisor

Committee Member for:

Jung-Mo Ahn	Mike Hadd	Qing Xu
Guoxia Han	Subo Liao	Jason Cox
Kathie McReynolds	Sam Phimphivong	Jason Imbriglio
Mark Turner	Ralf Voelkle	Shawn Allwein
Jeff Anthis	Jonathan Crumm	Jinfa Ying
Chiyi Xiong	Haofan Wang	John Ngungu
Son Lam	Hemant Joshi	Xuyuan Gu
Haiyong Gan		

Pu-Ping Lu (Prof. Ole Hindsgaul, advisor)
Synthetic probes of GlcNacT-V, a metastasis associated glycosyltransferase.
University of Alberta, Edmonton, Canada (1997)